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Brain lesion classification using 3T MRS spectra and paired SVM kernels

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ABSTRACT

The increased power and resolution capabilities of 3T Magnetic Resonance (MR) scanners have extended the reach of Magnetic Resonance Spectroscopy as a non-invasive diagnostic tool. Practical sensor calibration issues, magnetic field homogeneity effects and measurement noise introduce distortion into the obtained spectra. Therefore, a combination of robust preprocessing models and nonlinear pattern analysis algorithms is needed in order to evaluate and map the underlying relations of the measured metabolites. The aim of this work is threefold. Firstly we propose the use of a paired support vector machine kernel utilizing metabolic data from both affected and normal voxels in the patient's brain for lesion classification problem. Secondly we quantify the performance of an optimal reduced feature set based on targeted CSI-144 scans in order to further reduce the data volume required for a reliable computed aided diagnosis. Thirdly we expand our previous formulation to full multiclass classification. The long term aim remains to provide the human expert with an easily interpretable system to assist clinicians with the time, volume and accuracy demanding diagnostic process.

1. Introduction

Magnetic Resonance Spectroscopy (MRS) has been studied for more than a decade as a promising diagnostic tool for a variety of pathologies [1–4]. Coupled with the morphological features provided by Magnetic Resonance Imaging (MRI) techniques [5], it can provide accurate identification and quantification of biologically important compounds in soft tissue.

The transition of MRS from experimental evaluation studies to clinical practice relies heavily on the implementation and standardization of robust methodologies that decouple the diagnostic problem from inter and intra-patient variations, sensor calibration and procedural issues and the varying expertise of clinical personnel.

The classification problem itself is recognized as a nonlinear multiclass problem with varying difficulty depending on the specific class labeling [1,3,5]. In particular the partitioning of gliomas versus metastatic tumour classes is notably more challenging relative to other class pairs.

Additionally, a new generation of 3Tesla MRS scanners calls for adaptation of existing classification models, optimized on 1.5 T equipment, and evaluation of possible performance gains [6]. Regardless of the sensor technology used, the inter and intra patient variations of the collected spectra for each pathology class hinder the establishment of simple visual markers and outline the need for the development of adaptive nonlinear decision support tools.

Building upon our previous results [6–8] we propose the use of a SVM kernel that leverages the information conveyed by intra patient metabolite measurements. We also extend our analysis to full multiclass classification, utilizing an updated more extensive dataset of high resolution 3 T spectra obtained from patients at the Larisa University Hospital.

We additionally evaluate the use of a reduced metabolic feature set as an alternative to continuous spectrum classification in an effort to address practical compatibility, transferability and speed issues involved with the coupling of MRS scanners and clinical decision support systems. The utilized MRS scanner does not provide a well documented file access interface, therefore hindering automated high throughput access to the large volume of raw data obtained during each exam. Recording a minimal subset of exam metabolites circumvents this problem and evaluate their effectiveness as classification features.

The rest of this paper is organized as follows. Section 2 outlines the data mining and pattern analysis tools that we employ along with the proposed problem-specific SVM kernel. Section 3 provides an overview of the experimental results that we obtained on the Larisa MRS dataset and Section 4 summarizes the key findings and provides general guidelines and pointers to future research.

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2. Data mining and pattern analysis tools for MRS

2.1. Dataset and preprocessing

In order to verify the applicability of the proposed scheme the classification model was evaluated on a dataset collected at the MR Department, Larisa University Hospital, Greece using a GE Healthcare Signa® HDx MRS Scanner.

A total of 84 consecutive patients (age 8–77 years) under investigation of brain lesions (tumours, multiple sclerosis, gliosis, leukoencephalopathy, meningiomas, etc.) were enrolled in this study before any surgical biopsy and/or resection.

The typical proton MR spectroscopic features for the aforementioned lesions are NAA, Cho, Cre, mI, lipids and lactate. N-acetyl-aspartic acid (NAA) is present in the health brain parenchyma and is the highest peak in the normal spectrum, resonating at 2.02 ppm. The utility of NAA as an axonal marker is supported by the loss of NAA in many white matter diseases, including multiple sclerosis and leukoencephalopathy. Malignant tumours cause destruction of neurons and thus a loss of NAA and purely extra-axial tumours, such as typical meningiomas, demonstrate no NAA.

Choline (Cho) is a metabolic marker of membrane density and integrity, with its peak located at 3.22 ppm. Inta-axial and extra-axial tumours show an increase in the Cho peak because of increased cellularity. Increases in Cho relative to NAA are also noted in gliosis and multiple sclerosis. Therefore, difficulty may be encountered in interpreting results in some lesions, such as tumefactive multiple sclerosis.

In simplistic terms, Creatine (Cre) is a marker of "energy metabolism". The central peak on the spectrum at 3.02 ppm represents the sum of creatine and phosphocreatine. In the clinical setting, Cre is assumed to be stable and is used for calculating metabolite ratios (Cho:Cre and NAA:Cre ratios). It may be useful to note that Cre itself does not originate in the brain, and hence systemic disease (such as renal disease) may impact on Cre levels in the brain.

Myo-inositol (mI) is a simple sugar, with a peak found at 3.56 ppm. It is considered a glial marker. An increase in mI content is believed to represent glial proliferation or an increase in glial cell size, both of which may occur in inflammation. It is elevated in the setting of gliosis, astrocytosis, and in disorders such as Alzheimer's dementia. mI has also been labeled as a breakdown product of myelin present in tumourous lesions and multiple sclerosis.

Membrane lipids have very short relaxation times and are not usually visualized on intermediate or long TE, but are visualized on short TE. They produce peaks between 0.8 and 1.5 ppm and are usually large broad peaks. The presence of lipids may indicate voxel contamination by diploic space fat, scalp and subcutaneous tissues (when the voxel is placed near these structures). Lipid signals in pathology are generally associated with necrosis such as in high-grade brain tumours or metastases. In addition, lipid signals have been observed in brain MR spectra of patients with multiple sclerosis [9] and lipomatous meningiomas [10].

Under normal circumstances, lactate is present only in minute amounts in the brain and is not resolved using the normal spectroscopic techniques. However, under conditions where the aerobic oxidation mechanism fails and anaerobic glycolysis takes over, such as brain ischaemia, hypoxia, seizures, metabolic disorders, and areas of acute inflammation, lactate levels increase significantly. Lactate also accumulates in tissues that have poor washout, like cysts and necrotic and cystic tumours. When present, it is recognized as a doublet (twin peak) at 1.33 ppm. Lactate is characterized by variable projection of the peak at different TEs. On acquisitions using intermediate TEs (135/144 ms), the doublet peak is inverted below the baseline, but at very short or very long TE (30 or 288 ms), the doublet peak projects above the baseline [11].

All patients gave a written informed consent to participate in the study. 1H-MR spectroscopy studies were performed on a 3Tesla MRI whole body unit (GE, Healthcare, Signa® HDx) using both automated PROBE single voxel and multivoxel (Chemical Shift Imaging) spectroscopy packages before contrast administration.

Single Voxel (SV) spectroscopy was performed using the point-resolved spectroscopy (PRESS) pulse sequence, provided by the manufacturer at an echo time of 35 ms at axial, sagital and coronal planes. The repetition time was 1500 ms. Chemical Shift Imaging (CSI) was performed using PRESS pulse sequence, in an axial plane at an echo time of 144 ms and a repetition time of 1000 ms. The CS imaging slice was positioned in areas of maximum extension of the lesion.

In both cases of SV and CSI the regions of interest were defined as follows: (1) inside the lesion, (2) outer diameter of the lesion (if possible), (3) contralateral side, and (4) normal appearing white matter.

In cases of pathology we avoided inclusion of obvious necrosis, cyst, hemorrhage, edema, calcification and normal appearing brain tissue in the voxel, to avoid lesion's underestimation. Thus ROIs with potential contamination with cerebrospinal fluid, subcutaneous fat, or eye motion have been excluded from analysis.

For voxel positioning, fluid attenuated inversion recovery (FLAIR, TR = 9502 ms, TE = 128 ms) or a home-designed T2-weighted fast spin echo (TR = 4520 ms, TE = 102 ms) sequence in axial, coronal and sagittal planes were preceded using 26 cm field of view, 5 mm slice thickness and NEX equal to 1. The size and location of the voxels were carefully adjusted inside the lesion or in healthy brain parenchyma for the best possible shimming and spectra accuracy. The exact voxel positioning protocol is indicated in Fig. 1. Due to data quality and availability limitations the resulting features used for classification included spectral measurements from areas 1 (inside the lesion) as pathological and 3 (contralateral) as normal. The features (metabolite measurements) obtained from each area were utilized either as a single feature vector or separately as part of the proposed composite kernel, described in Section 2.2.

The MRS sensor data were preprocessed using standard statistical methods for outlier detection, normalization and peak integration. Peak integration was performed in the ranges 3.35–3.17 ppm (choline), 3.15–2.99 (creatine), 2.23–1.97 (NAA), 3.02–3.31 (creatine + choline), 1.30–0.90 (lipids and lactate) and 3.69–3.54 myolnositol.

The diagnostic class labelings were obtained from three sources (1) histological examination (where available), (2) radiologist expert assessment, and (3) physicist's expert assessment. Histological data were available for only ~42% of the patients. The resulting confusion matrices indicated a full agreement of the radiologist's and physicist's class labelings whereas there are notable differences between the above labelings and histological class labeling for the given patient subset. The correspondence between the radiologist diagnosis and histological results are shown in Fig. 2. Despite the fact that histological evaluation results are considered the gold standard, the final classification system's training was performed using the radiologist's diagnosis due to the extensive data missingess of the histological labelings. Under this prism, the proposed model is at this phase evaluated from the aspect of optimally mapping a radiologist's diagnostic behavior. This classifier is intended as a primary expert mapper to be integrated in the future in a multi classifier system that will simulate a committee of clinical experts.

Since brain tumour classification is inherently a multiclass problem, one has to resort to techniques that allow for handling such problems with a pool of classifiers that provide binary outcomes. There are numerous approaches to multiclass mapping in litera-